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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,379	CASTANEDO ET AL.	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims **1-29** are pending and are presently under examination.

Specification

Priority date for this invention, applied under 35 USC §119 (a-d) for the Foreign application SPAIN 200202815 filed on 12/09/2002.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8, 14-20, 22-29 are rejected under35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

Claim 1-8, 14-20, 22-29 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol.66, No. 4, pp.1092-1099 (January 5, 2001), also available as repeated below from http://www.uspto.gov/web/menu/utility.pdf, the following definition of credible, specific and substantial utility.

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is

credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the specific and substantial tests (see below).

"Specific Utility"- A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method .of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a specific or substantial utility. For example, using transgenic mice as snake food is a utility that is neither specific (a11 mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context an; nature of the invention. For example, if a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for ' specific and substantial asserted utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paperweight', any

carbon containing molecule would have a "well established utility" as a fuel since it can be burned', any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP § 2107 - 2107.02, and Brenner, Comr. Pts. V. Manson, 148 USPQ 689 (US SupCt 1966).

Instant claims are directed to a transgenic mouse and a method of making said mouse, and methods of using said mouse comprising a disruption in an endogenous Sigma 1 receptor gene, wherein the disruption is homozygous wherein the phenotype of mutant mouse was indistinguishable from wild type mouse with exception of a marginal insensitivity to (+)SKF-10047-induced hyperactivity assay.

The specification of the instant application discloses mice which have a homozygous disruption in endogenous the Sigma 1 receptor gene and absence of a overt phenotypic difference in said mutant mouse relative to wild type controls except for a marginal insensitivity to (+)SKF-10047-induced activity assay. Phenotype does not correlate well with any of the art-anticipated role of Sigma receptor proteins. The art teaches that the members of Sigma receptor family are associated with various physiological and pathological conditions including CNS pathologies such as schizophrenia, amnesia and learning and memory deficits as well as other types of psychiatric disorders, (Maurice et al., 1997, Prog. Neuro Psychopharmacol and Biol. Psychiat. 21:601-102, see abstract; Prasad et al., 1998, J. Neurochem. 70:443-451, see abstract). The specification fails to provide any nexus between the asserted phenotype and any disease or conditions that would enable one skilled in the art to use the invention as claimed.

Thus at the time of filing of the instant application, the artisan would not have found claimed utilities evident because the art is devoid of any teachings for the role of specific function for the sigma receptor I gene other than the ones anticipated as above for the members of sigma receptor family. Since the mice disrupted Sigma I receptor homozygous mice are not specific to any one disease or condition, the artisan, at the time of filing, would not know how to use the mice or any data resulting from using the mice for substantial and specific purpose.

As set forth in the utility guidelines above, a general statement of therapeutic utility for an unspecified disease is non-specific, renders the purported utility of the claimed mice to be non-specific. The usefulness of the mutant mice, as models for disease, is not clear absent the assessment that they reflect a particular disease state. This leaves the skilled artisan to speculate the uses of the mice, cells, and methods, as claimed. Under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility.

Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are not considered substantial utilities. The evidence of record has not provided any other utilities for the transgenic mice encompassed by the claims that are substantial and specific. Since the mice have no determined specific function, the relation to any disease or condition is unknown, and further, because the phenotypes in the disrupted Sigma receptor I-homozygous mice are not specific to any one disease or condition, the artisan, at the time of filing, would not know how to use the mice or any data resulting from using the mice. To make such a determination, the skilled artisan would need to further research the mice, to determine if functions associated with Sigma receptor I are present in 'the mice, and then identify disease or conditions associated with the disclosed phenotypes. None of the asserted utilities of the transgenic mice comprising Sigma receptor I gene disruption, cells and tissues derived from the same, and methods of producing the same, appear specific and substantial, because they do not correlate to the art anticipated role/s of Sigma receptor I gene.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claim 1-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

Instant claims are directed to a transgenic non-human mammal with a homozygous or heterozygous mutation comprising gene-disruptions in a gene belonging to the genus of endogenous Sigma receptors and to a cell or tissue obtained from the same and cultured in vitro, to a method or process of making a transgenic non-human mutant mammal comprising a disruption of an endogenous Sigma I receptor gene, to a targeting construct for disrupting the gene belonging to sigma receptor 1 & genes gene, to a method of using said mutant mouse for evaluating potentially useful compounds for treating or preventing a CNS disorder, stress conditions, to a method determining the effect of a compound on said non human-mammal or a cell derived from said mammal,

The scope of the claims encompasses any and/or all non-human mutant mammals (mouse, cat, whales, ... etc) that are deficient in any and/or all endogenous Sigma receptors (e.g. Sigma receptor 1-3 etc), any vector that could be used for homologous recombination for making said nonhuman-mutant mammals, any cell derived from said mammals. By the breadth of the generic claim for "an endogenous sigma receptor gene" the applicants attempt to encompass genes including coding sequences, regulatory sequences, introns etc of all the members of Sigma receptor family and all possible ways of obtaining a mutant non-human mammals with said mutations comprising genes disruptions.

At the best specification describes a single example of a mouse with mouse Sigma I gene disruption, a single method generating said mutant mouse, a single vector construct for generating said mouse (Example 1-2). The specification further limits to a conventional gene-targeted endogenous Sigma I receptor gene generated by a

conventional method of gene targeting and using a conventional gene targeting vector construct with an art established gene Sigma I receptor gene sequences (Example 1-2 and figures). The specification further describes Sigma I gene and protein expression in various organs of a heterozygous and homozygous mutant mice has been described (Example 2 and figures), binding assays and a behavioral evaluation is carried out. The only mentioned phenotypic difference between wild type mouse and the homozygous mutant mouse was with reference to a difference in hyperactivity activity assay in response to SKF-10047 (data is not shown in the specification).

Besides mouse the specification does not describe any other mutant non-human mammals that are disrupted in any sigma receptor genes, does not describe any targeting vectors other than a single one for a mouse sigma receptor gene, does not describe any other method of making a Sigma receptor mutant animal other than a art established conventional method of gene targeting, does not describe culturing any mutant cells or their useful properties, does not describe any of the broadly claimed methods of utilizing the mutant for evaluation of any useful compounds for preventing or treating any disorders of CNS or memory alteration or stress conditions or producing analgesia or neuro-protection, does not describe any method of utilizing Sigma receptor-2 other sigma receptor gene mutant non-human mammals for validating or developing any drugs for diagnosis or treatment of cancer or for preventing, reducing or alleviating any side effects due administration of any neuroleptic agents, does not sufficiently describe the methods of determining the effect of any compounds on broad claims to mutant non-human mammals or the cells derived from the same. Specification does not describe any Sigma receptor gene mutant non-human mammal possessing any significant phenotype that would enable the use of any said mutant non-human mammal to serve as a model for any art established human/animal diseases or human/animal conditions.

Since the disclosure fails to describe the common attributes or characteristics that identify representative number of members of the said genus non-human mammals or their significant phenotypes or the methods of making and using the same for the broad claims of utility as described above one skilled in the art would reasonably

conclude that the disclosure fails to provide a representative number of species to describe the genus. The claimed invention as a whole thus not adequately described in the specification and which is not conventional in the art as of applicants' effective filing date. Claiming all divergent species that achieve a result as contemplated by the application without defining the means and/or uses will do so not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. "The written description requirement has several policy objectives. The essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998)."

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (January 5, 2001 Fed.Reg., Vo.66, No. 4, pp. 1099-11).

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse a mouse with a Sigma I gene disruption carried out using a conventional method of gene targeting with a conventional gene targeting construct vector construct for mouse Sigma I receptor gene, does not provide enabled description of targeting of any other sigma receptor genes and in any other mammals besides mouse or their use. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Since the specification fails to disclose any other mutant mammals with any sigma receptor genes, or their phenotypes or uses. The applicant's disclosure does not

enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation, which requires the construction and characterization of any and all mutant mammals with a disruption in any and all sigma receptors. At issue, under the enablement requirement of 35 U.S.C.112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

Claims 1-8 and 14-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through "undue experimentation" in order to practice the invention.

Nature of the invention: The invention relates to Sigma receptor mutant non-human mammals, method of generating said mutant non-human mammals and methods of utilizing said mutant non-human mammals and/or the cells derived from the same for evaluating compounds useful for treatment of CNS disorders and other conditions described above.

Breadth of the claims And Guidance of the Specification and The scope and breadth of the instant claims, read in the light of instant specification and the state of the art at the time of filing encompass methods of making any non-human mutant mammal comprising a disruption in any and /or all Sigma receptor genes and utilizing said non-human mutant mammals with said mutation in any and/or all genes belonging to genus Sigma receptors for evaluating any and/or all compounds for their potential in preventing or treating any and/or all disorders of the CNS or memory alterations or stress conditions or drug addictions in any subject and further encompasses the use of said mutant non-human mammal in validating and developing drugs for diagnosis or treatment of any cancer or any degenerative processes in any subject and still further encompasses methods for preventing or reducing or alleviating any side effects associated the administration of any and/or all agents that are neuroleptic and methods for conducting any and/or all further biological research on sigma receptors.

With respect to instant claims the specification provides by means of specific examples guidance and/or evidences regarding a single example of a mouse with Sigma I gene disruption. specification further limits to a conventional gene-targeted endogenous Sigma I receptor gene generated by a conventional method of gene targeting and using a conventional gene targeting vector construct. The only mentioned phenotypic difference between wild type mouse and the homozygous mutant mouse was with reference to a difference in hyperactivity activity assay in response to SKF-10047 (data is not shown in the specification).

Specification does not enable any mutant non-human mammals that are disrupted in any sigma receptor genes, does not enable the Sigma 1 receptor targeted mouse as it lacks a substantial use, does not enable any sigma receptor targeted mutant cells as they lack a substantial use, does not enable any of the broadly claimed methods of utilizing the mutant for evaluation of any useful compounds for preventing or treating any disorders of CNS or memory alteration or stress conditions or producing analgesia or neuro-protection, does not describe any method of utilizing Sigma receptor-2 other sigma receptor gene mutant non-human mammals for validating or developing any drugs for diagnosis or treatment of cancer or for preventing, reducing or

alleviating any side effects due administration of any neuroleptic agents, does not provide sufficient enablement for the methods of determining the effect of any compounds on broad claims to mutant non-human mammals or the cells derived from the same. Specification does not describe any Sigma receptor gene mutant non-human mammal possessing any significant phenotype that would enable to serve as a model for any art established human/animal diseases or human/animal conditions.

The specification thus fails to provide an enabling disclosure for the full scope and breadth of the invention as claimed. In the absence of adequate description of the enabled invention commensurate with the breadth and scope of the claim one of ordinary skill in the art would conclude that the claimed invention is unpredictable and would require an undue amount of experimentation to practice the full scope of the same. Applicants' attention is drawn to In re Shokal, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). The test is whether the species completed by applicants prior to the reference date or the date of the activity provided an adequate basis for inferring that the invention has generic applicability.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

***State of the Art, the Predictability of the Art*:** At about the effective filing date of the present application art does not provide enablement for making a gene disrupted gene knockout mutant non-human mammal other than in mouse species. Gene targeting method as described for a mouse Sigma I receptor gene as described in the instant invention is only enabled for mouse. Art is still unpredictable with regard to achieving a desired phenotype even in a mouse that is of substantial use or utility for example modeling human/non-human animal diseases or conditions. Holschneider et al. Int J. Devl. Neuroscience 18:615-618, 2001, state that knocking out or insertion of a single gene may result in no phenotypic change. This may be the case, in particular, if there exist gene redundancy mechanisms whose presence may prevent abnormal

phenotypes from becoming expressed. Conversely, single genes are often essential in a number of different behaviors and physiologic processes. Silence, ablation of an individual gene may prove so drastic as to be lethal, or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interactions of the various new physiologic changes or behaviors." (See p. 615, col. 1-21. Holschneider et al., discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory systems which may be activated to mask the resulting phenotype, these compensatory changes may be due to the differential expression of another gene, which may be regulated by the downstream product of, the ablated gene, as well as the variability in phenotypic characterization due to particular mouse strains (see p. 616, 1st column. Even the conventional targeting approach, as is in the instant application, has limitations including functional redundancy of closely related proteins, induction of compensatory processes and early embryonic lethality (Holschneider et al., Int. J. Devl. Neuroscience 18:615-618, 2000; see p. 616, 1st col. 2nd ¶).

It is noted that specific claims are presented, which are directed to cells/tissues obtained from the transgenic mice (see claims 4 & 8). These claimed cells will not have the phenotypes claimed for the mice, and thus, it is unclear what or any phenotype these cells exhibit. Therefore, the contemplated uses of these cells, such as for screening any drugs/compounds is not enabling. The instant specification is not found to be enabling, because there is a lack of a siginificant phenotype in Sigma I receptor gene disrupted mouse of the instant invention that can be correlated with any known disease or disorders of humans or animals of economic interest.

There is no nexus between this phenotype and art contemplated functions of Sigma receptors such that one of skill in the art could make and use these mice in any of the contemplated uses as claimed. The art regarding the function of the Sigma receptors teaches that. In the light of unpredictability and lack of guidance in the art it requires undue experimentation for one skilled in the art to know the correlation, if any, exists between the observed phenotype of a marginal decrease in hypermotility in response to prozocine.

Furthermore, there is unpredictability in the art with regard to the resulting less significant phenotypes because of the possibility that such variations are due to differences genetic backgrounds of mouse strains used in breeding to generate the homozygous gene disrupted mice as it is in the instant invention. It is well established in the art, the homozygous mice claimed will have some129/Sv genes, regardless of the outward appearance of the mice, due to the 129-knockout construct. F2 mice homozygous for the disrupted Sigma I receptor gene have genotypes from two parents, 129/Sv and C57BL/6 or 129Sv and CD-1 due to recombination events during gametogenesis (Gerlai, G. et al. Trends in Neuroscience. 19: 177- 181 (1996), specifically page 178, lines 1-5). These mice are genotypically different from wild-type littermates, and thus wild-type littermates are not good controls for the null mice (Gerlai, page 178, col. 1, lines 6- 18). This effect causes linkage disequilibrium between the transgene and surrounding genes, producing a "hitchhiking donor gene confound" (Lariviere et a1. J. Pharmacology Experiment. Therapeut. 297: 467-473 (2001), particularly, page 468, col. 1, 2nd ¶, lines 1-4). To overcome the "hitchhiking effect, two remedies are suggested: testing a large number of mice (Gerlai, page 178, col. 2, lines 1-5) and many backcrosses (Lariviere, page 468, col. 1, 2nd ¶, line 18-21). However, even with a large testing population and multiple backcrossings, some of the 129/Sv1 genome will remain. Thus, the behavioral and physiological effects observed in the presently claimed Sigma receptor 1 null mice could be due to 129/Sv1 gene background (Gerlai, page 179, col.1, lines 9-14). There is no way to tell given the tests in the disclosure. Further there does exist genetic heterogeneity with regard to lipoprotein levels in inbred strains of mice (see Cole et al., Metabolism, 1990, 39:155-160, p.155, 1st¶, abstract)). Given this unpredictability and in the absence of guidance in the specification one of skill in the art will find it unsubstantial and hence unable to practice the invention for any specific purpose.

These claims are not enabled because one of skill in the art would not be able to produce any non-human mutant mammals, as instantly claimed, exhibiting consistent phenotype with art contemplated function for Sigma receptors, and further, one would not be able to use these mutant non human mammals for a substantial use, since they

do not exhibit these phenotypes. One of skill in the art would not be able to rely upon the state of the art in order to produce Sigma 1 mutant non-human mammal other than in mice and would not be able produce a mice with a phenotype for a substantial use as claimed, because, for reasons stated above, because of the unpredictability in the resulting phenotype of any particular knockout mouse. Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to an enabled use for a mouse comprising a disruption in an endogenous Sigma receptor gene, absent guidance provided by the specification to overcome the art-recognized unpredictability regarding gene disrupted mice and lack of technology to produce other gene disrupted non-human mammals, and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-21and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (U.S. Pat. No.5,464,764) in view of Seth et al., (2000, Biochemical and Biophysical Research communications 241: 535-540).

The claims are directed to a homologous recombination vector for a Sigma receptor gene with a positive and negative selection marker and a first and second homology region of said gene, a host cell transfected with said vector, a non human mutant mammal deficient (targeted) endogenous Sigma receptor gene, a process of making a non-human mutant animal.

Capecchi teaches a vector to be used to produce knockout mice. Particularly, that the vector has a first and second segments of homologous DNA sequence, and a positive selection marker between the two homologous sequences. See Figure 1.

Furthermore, they teach various markers that can be used in these vectors (Table 1. col.7-8). They teach that these vectors can then be used to produce transgenic animals, wherein ES cells are the target cells (Col. 15, lines 59-67), wherein the vector can then be introduced into the ES cells by electroporation or microinjection. These transformed ES cells can then be combined with a blastocysts and then grown and contribute to the germ line of the resulting chimeric animal (Col. 16, lines 1-10). They teach that cell lines from the animals can then be used to characterize gene function, or be used in assays (Col. 12-13, bridging paragraph). Capecchi clearly show that these vectors and methods can be used to determine the biological function of any known gene of interest. Capecchi however, does not teach the sequence for Sigma receptor gene.

Seth teaches that cDNA sequence of Sigma I receptor (Abstract, p.536). Known sequence, which would fulfill the limitations of the claims, because this sequence would be considered homologous to at least a portion of the endogenous Sigma receptor gene (p.538 and Figure 2).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the homologous sequences in targeting vectors as taught by Capecchi with segments of DNA sequence for Sigma I receptor as taught by Seth to make a targeting construct and use the construct to generate a gene disrupted mouse, and further breed them to generate a homozygous gene disrupted mouse where the genome of the mouse comprises a homozygous disruption of a Sigma receptor I gene. One would have been motivated use the method making a targeting vector and for producing mice having a homozygous disruption of sigma receptor gene as they may provide a disease model for investigating the art described diseases or conditions associated with sigma receptors malfunctions. One would have a reasonable expectation of success of making and using Sigma receptor gene disrupted mouse as prior art provides the requisite teaching, suggestion and motivation to make and use the claimed invention as taught by Capecchi and Seth as above.

Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at **(571) 272-0731.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

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